PATENT
3657-1025

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Enok TJOTTA Conf. 5328

Application No. 10/530,488 Group 1642

Filed April 6, 2005 Examiner Peter J Reddig

METHOD FOR SELECTION OF COMPOUNDS WHICH INHIBIT CLONAL CELL GROWTH AND USE THEREOF

DECLARATION

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Enok TJOTTA, a named inventor, am a citizen of Norway and reside at c/o Hoyenhallsvingen 23, N-0667 Oslo, Norway.

2. I am familiar with the above-identified U.S. patent application, its prosecution before the United States Patent and Trademark Office, and the applied art references.

3. In order to demonstrate the patentability of the present invention, I am submitting the following observations.

Independent claims 28 and 61 have been amended to add an additional step: "*a) selecting an agent selected from the group consisting of 4-OH-OPB, drugs, food, food additives, toxins, and*

microbes, or components from physiological or pathological processes, where said agents or components demonstrate specific inhibition or specific stimulation of clonal growth in only ***sparsely*** *distributed cells, not in collocated areas of identical cells."*

It is respectfully submitted that the applied art alone or in combination does not anticipate or render unpatentable independent claims 28 and 61 of the present invention.

Particularly HOWELL et al. do not disclose or infer the use of 4-OH-OPB and do not seed their cells sparsely as in the sense of the present invention where a cell density gradient in agar culture made it possible to compare the effect on both sparsely and densely distributed cells in the same culture.

Moreover, the inventor of the present invention, Dr Tjøtta, has studied the applied art and wishes the submit of the following observations.

The invention of HOWELL et al. sets forth a method of sensitizing various types of cancer cells derived from different tissues of origin to various cytotoxic agents and augmenting the sensitivity of cancer cells to these cytotoxic agents. The invention provides a method to treat cancer and other cell proliferative diseases by the administration of a sensitizing

agent prior to or concurrently with the administration of a cytotoxic agent.

This is not the aim of my patent application:

1. Cytotoxic agents are not examined or included in any claim.

2. Only compounds that inhibit or stimulate growth of cells (normal, transformed (experiment no. 5)), cancer cells (experiment no. 7-9) or immune cells (experiment no. 10) that are seeded sparsely in soft agar (experiment no. 5) or that are mixed with other cells of other specificities (as the immune cells of the spleen (experiment no. 10)) or cells going to develop cancer (see last paragraph on page 42 and first paragraph on page 43) or cells going to spread from a malignant tumor in an individual (experiment no. 9) are included.

Technically HOWELL et al. seed their cells sparsely at about 4000 cells in one ml in dishes of 3.5 cm in diameter, ***but they did not compare the effect of the studied compounds on sparsely seeded cells with the effect in collocated ~~cell~~ areas of identical cells.*** In my experiments, however, often between 35000 and 144000 cells were seeded in wells of 15 mm in diameter in 0.3 ml top soft agar layer on a bottom agar layer of 0.3 ml.

The top layer containing the cells was placed on a bottom layer cast at an oblique angle of about 12 degrees in order to create a cell density gradient in the top layer.

The cell density gradient on the side of the well with the minimal cell number contained only about ¼ of the total cell number of the well. However, the most sparsely distributed cell area on the same side of the well only contained very few cells.

This gradient made it possible to compare the effect on cell growth induced by a compound on both sparse and crowded areas in the same well. I only looked for compounds with specific inhibition or stimulation only on cells that were sparsely seeded and not on collocated identical cells.

In addition I cannot find HOWELL et al. using 4-OH-OPB, the definitely best compound detected by the method described in my invention (published as WO 2004/055175 A1). 4-OH-OPB was the only compound among the studied ones that was able to rescue mice transplanted with Ehrlich carcinoma and completely stop the development of metastases (experiment no. 7-9). However, if the transplantable Ehrlich cancer developed tumors, 4-OH-OPB had no inhibiting effect on their growth (experiment no. 9).

There are no indications either that 4-OH-OPB may be a sensitizing agent as described by Howell et al.

Cytotoxic agents are mentioned by me in connection with a quite different field. Since 4-OH-OPB stops the development of new clones (experiment no. 13), also tumor clones resistant to cytotoxic agents are expected to be included. Therefore, the effect of treatment with cytotoxic agents ~~are~~ also is expected to last longer before ~~they loce~~ loosing activity against a malignant disease if 4-OH-OPB is given simultaneously.

4. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date February 9th 2011.

Enok TJOTTA